Carotid intima-media thickness and related factors in chronic kidney disease

Chronic kidney disease and atherosclerosis

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Abstract

Aim: Cardiovascular diseases are the most important cause of mortality. Evaluation of atherosclerosis is important to prevent the development and progression of cardiovascular disease. Carotid intima-media thickness (CIMT) is an indicator of generalized atherosclerosis. In this study, we aimed to examine CIMT and related factors in CKD.

Material and Methods: The study was conducted with the patients who applied to the Nephrology outpatient clinic. The control group consisted of healthy volunteers. Patients over 18 years of age with a diagnosis of CKD, without active infection, without malignancy, without obesity, without lipid and uric acid-lowering medication, without thyroid hormone replacement, and without uncontrolled hypertension were included in the study. The CIMT of the patients and their laboratory and demographic data were compared statistically.

Results: Proteinuria in patients increased with increasing stages, and no significant difference was found between the CIMT values. The risk of atherosclerosis increased approximately 4 times over the age of 60, and the risk increased approximately 2.5 times in the presence of proteinuria above 500 mg/day.

Discussion: Our study has shown that the presence of proteinuria, independent of GFR in CKD increases CIMT and thus cardiovascular mortality. We think that evaluation of patients with CIMT may be important for early diagnosis of cardiovascular events, especially in elderly patients with proteinuria.

Keywords

Atherosclerosis; CIMT; CKD; Proteinuria

Introduction

Chronic Kidney Disease (CKD) is a serious public health problem with high mortality and morbidity all over the world [1]. Cardiovascular diseases are the most important cause of mortality. Despite advances in the management of cardiovascular diseases in the last 40–50 years, the risk is still high in patients with end-stage renal disease (ESRD) [2–5]. The risk occurs from the early stages of CKD [6,7]. Traditional atherosclerosis risk factors such as age, increased blood pressure, diabetes mellitus (DM), lipid disorders, obesity and tobacco use habits revealed in epidemiological studies such as the Framingham study cannot fully explain early-rapidly developing atherosclerosis and its associated high morbidity and mortality rate in CKD. In addition to traditional risk factors for atherosclerosis, novel risk factors associated with uremia are thought to play an important role in the development of early-onset and rapidly progressing atherosclerosis in the CKD process. Therefore, the evaluation of atherosclerosis is important to prevent the development and progression of cardiovascular disease [8,9]. Carotid intima-media thickness (CIMT) is an indicator of generalized atherosclerosis. It is an easy, non-invasive, inexpensive and reproducible method to measure CIMT using ultrasonography. In recent years, there have been studies showing the relationship between CIMT, atherosclerosis and cardiovascular events in CKD, but no consensus has been reached yet [10–13]. In our study, we aimed to examine CIMT and related factors in CKD.

Material and Methods

The study was conducted with patients who applied to the Nephrology outpatient clinic. The study was conducted with the necessary permissions from the Istanbul Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (Dated 14.01.201 and numbered 2021.01.235). The study was conducted according to the recommendations of the Human Subjects Biomedical Research Helsinki Declaration. Patients who wished to participate in the study voluntarily were included. Demographic characteristics such as age, gender, drug use were questioned. Blood pressures were measured with the same sphygmomanometer in a sitting position in a quiet room, and the results were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP) (in mm/Hg). Pulse rate, Body Mass Index (BMI) of the patients were recorded. The study included patients over 18 years of age with a diagnosis of CKD, with no active infection, with no malignancy, no obesity, no lipid and uric acid-lowering medication, no thyroid hormone replacement, and with no uncontrolled hypertension. The control group consisted of healthy volunteers.

Biochemical Analysis:

Complete blood count (hemogram), blood urea nitrogen (BUN, mg/dl), creatinine (mg/dl), sodium (Na, mmol/l), potassium (K, mmol/l), calcium (Ca, mg/l). dl), phosphorus (P, mg/dl), magnesium (Mg, mg/dl), uric acid (mg/dl), albumin (g/dl), total protein (gr/dl), total cholesterol (mg/dl), triglyceride (TG, mg/dl), low density lipoprotein (LDL, mg/dl), high density lipoprotein (HDL, mg/dl), c-reactive protein (CRP, mg/l), ferritin (ng/ml), free triiodothyronine (FT3, pg/ml), free thyroxine (FT4, ng/dl)

and thyroid stimulating hormone (TSH, µIU/ml), 25 OH vitamin D (ng/ml) and parathyroid hormone (PTH, pg/ml) values were measured. Protein excretion in patients was calculated by dividing the spot urine total protein amount by the spot urine amount of creatinine. The glomerular filtration rate (GFR) was calculated using the MDRD formula. (MDRD formula = 170 x (serum Cr) - 0.999 x (age) - 0.176 x (0.762 if the patient is female) x (1.180 if the patient is black) x (serum BUN) -0.170 x [(Albumin) + 0.318]). Complete blood count was studied in 3700 CELL DYN device with an autoanalyzer method. BUN, creatinine, Ca, P, Mg, uric acid, albumin, total protein, total cholesterol, TG, LDL, HDL, total protein in spot urine, and creatinine were studied using photometric Beckman Coulter preanalytical and modular system (UniCel Dxc 800) device. With the sodium and potassium ISE method, Beckman Coulter preanalytical and modular system (UniCel Dxc 800) was studied. CRP was studied using the nephelometric method on the Beckman Coulter preanalytical and modular system (IMMAGE 800). FT3, FT4, TSH and PTH were studied on the Abbott Architect i2000 device using the imunokemiluminasan assay method. Hemogram analysis was done automatically on Beckman-Coulter device, ferritin analysis was performed in Hitachi E170 device, 25 OH vitamin D analysis was performed with Trinity Biotech Captia Reader device.

Measurement of Carotid Intima-Media Thickness (CIMT):

All subjects were in supine position, and the anterior neck was fully exposed, with the head back. Two separate measurements were made on the left common carotid artery and the right common carotid artery (1 cm proximal to the bulbus), and the average of these two measurements was taken. No measurements were taken in places where atheroma plaques were visible. Carotid artery intima-media thickness was evaluated between two echogenic lines seen between the intima-lumen interface and the media-adventitia interface. The mean carotid artery intima-media thickness was calculated by dividing the sum of the right and left carotid artery intima-media thickness into two. CIMT was measured in the Radiology Outpatient Clinic of Istanbul Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital using the B mode of Mindray DC-7 device. The cut-off value for CIMT was 0.75 mm [14].

Statistical analysis:

The data were recorded and analyzed using IBM SPSS Statistics version 22.0 package program. Conformity of the variables to the normal distribution was examined by visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were performed using means and standard deviations for normally distributed variables. While analyzing the data, independent groups t- test (Student's t-test) was used to compare the two groups, and the Mann-Whitney U test was used if the conditions were not met. With one-way analysis of variance and the Tukey HSD test, one of the multiple comparison tests, for comparin three or more groups; when the conditions were not met, the Kruskal Wallis and Bonferroni-Dunn test from multiple comparison tests were used. The Chi-square and Fisher Exact's tests were used in the analysis of categorical data. The statistical significance level was accepted as p<0.05.

Results

A total of 95 patients (51 females (53.7%), 44 males (46.3%) and (41%) total 22 healthy volunteers (13 females (59%), 9 males) were included in the study. The mean age of the patients was 59.5 ± 13.9, while the mean age of the control group was 34.8 ± 9.7. In comparison of control group and patient group, age, BUN, creatinine, phosphorus, uric acid, triglyceride, CRP, PTH, ferritin, right CIMT, left CIMT and mean CIMT values were found to be statistically significantly higher in the patient group, and the levels of calcium, albumin, FT3 values were statistically significantly lower.

In the evaluation of the patients according to the CKD stages, 40 patients were Stage-3 (42.1%), 33 patients were Stage-4 (34.7%), and 22 patients were Stage-5 (23.2%). When the patients were compared according by their stages, no significant difference was found in terms of age, disease duration and comorbid diseases. As the stage progresses, the levels of Calcium, phosphorus, CaXP of the patients were found to be high, albumin and hemoglobin levels were low. While the proteinuria of the patients increased with increasing stages, no significant difference was found between the CIMT values.

Patients with and without DM and coronary artery disease (CAD) were compared. While there is no significant difference between CIMTs of patients with and without DM regardless of the stage, when the patients with CAD were evaluated, CIMTs were found to be significantly higher (Table 1).

Patients were divided into two groups according to CIMT. Those with CIMT greater than 0.75 mm and those below were compared. In the group with CIMT above 0.75 mm, age, female gender and proteinuria were found to be significantly higher (Table 2).

Table 1. Comparison of the patients according to the presence of Diabetes Mellitus and Coronary Artery Disease

	Diabetes Mellitus			Coronary Artery Disease		
	+	-	p	+	-	p
All Stages						
Right CIMT (mm)	0.65±0.14	0.62±0.18	0.236	0.71±0.18	0.59±0.15	0.003
Left CIMT (mm)	0.69±0.18	0.67±0.23	0.376	0.78±0.22	0.63±0.19	0.002
Mean CIMT (mm)	0.67±0.16	0.65±0.20	0.280	0.74±0.19	0.61±0.17	0.002
Proteinuria (gr/day)	2.36±2.3	1.18±.15	0.003	1.97±2.5	1.43±1.6	0.968
Stage 3						
Right CIMT (mm)	0.67±0.20	0.63±0.09	0.664	0.67±0.17	0.56±0.09	0.157
Left CIMT (mm)	0.73±0.26	0.66±0.13	0.790	0.73±0.23	0.56±0.11	0.157
Mean CIMT (mm)	0.70±0.22	0.65±0.10	0.834	0.70±0.20	0.56±0.09	0.113
Proteinuria (gr/day)	0.52±0.84	1.52±1.71	0.023	2.1±2.5	0.67±0.9	0.183
Stage 4						
Right CIMT (mm)	0.66±0.17	0.60±0.19	0.213	0.740±0.15	0.58±0.17	0.022
Left CIMT (mm)	0.70±0.22	0.64±0.21	0.345	0.79±0.18	0.62±0.21	0.055
Mean CIMT (mm)	0.68±0.19	0.62±0.19	0.258	0.76±0.17	0.60±0.18	0.028
Proteinuria (gr/day)	1.07±1.2	2.42±1.7	0.016	2.1±2.1	1.4±1.2	0.470
Stage 5						
Right CIMT (mm)	0.68±0.19	0.57±0.13	0.212	0.67±0.24	0.59±0.12	0.494
Left CIMT (mm)	0.71±0.22	0.61±0.14	0.267	0.73±0.23	0.62±0.15	0.261
Mean CIMT (mm)	0.69±0.20	0.59±0.13	0.212	0.70±0.23	0.60±0.13	0.294
Proteinuria (gr/day)	3.71±3.3	2.59±2.2	0.402	4.65±3.3	2.4±2.1	0.098

CIMT: Carotid Intima Media Thickness

Diagnostic decision-making features in predicting subclinical atherosclerosis for proteinuria and age were examined with the ROC curve. The cut-off value for age was found to be 60 with 72.2% sensitivity and 64.4% specificity. This value for proteinuria was found as 500 mg/day with 64.4% sensitivity and 68.2% specificity (Figure 1, Table 3). As a result of the logistic regression analysis, it was shown that the risk of atherosclerosis increased approximately 4 times over the age of 60, and the risk increased approximately 2.5 times in the presence of proteinuria above 500 mg/day (Table-3).

Table 2. Comparison of patients according to Carotid Intima Media Thickness

	CIMT ≥ 0.75 mm (n=36)	CIMT < 0.75 mm (n=59)	p
Age (years)	66.6±10.5	55.1±14.1	<0.001
Gender (F/M)	13/23	38/21	0.007
Disease Duration (years)	4.9±3.8	4.5±2.6	0.806
Stage 3-4-5	18/10/8	22/23/14	0.430
HT	33/3	54/4	NA
DM	12/24	22/37	0.696
CAH	18/18	12/47	0.003
BUN (mg/dl)	41.9±17.4	41.7±19.6	0.573
Creatinine (mg/dl)	2.7±1.7	3±1.8	0.297
GFR (ml/min)	27.6±13.6	25.2±12.9	0.405
Calcium (mg/dl)	9.2±0.7	9.1±0.7	0.340
Phosphorus (mg/dl)	3.8±0.8	4±1.2	0.470
Ca x P	34.5±6.5	36.4±9.8	0.594
Proteinuria (gr/day)	1.9±2.1	1.1±1.6	0.024
CRP (mg/l)	3.8±3.6	4.9±4.9	0.487
Hemoglobin (gr/dl)	11.7±2.3	11.4±2	0.539
Uric Acid (mg/dl)	6.6±1.5	6.3±1.4	0.203
T. Cholesterol (mg/dl)	179.4±40.9	185.6±42.6	0.607
Triglyceride (mg/dl)	168.2±82.6	196.6±173.5	0.994
HDL (mg/dl)	42.1±10.4	44.5±13.1	0.429
LDL (mg/dl)	104.1±34.2	106.7±31.8	0.918

HT: Hypertension, DM: Diabetes Mellitus, CAH: Coronary Artery Disease, BUN: Blood Urea Nitrogen, GFR: Glomerular Filtration Rate, CaxP: Calcium phosphorus product, CRP: C Reactive Protein, HDL: High- Density Lipoprotein, LDL: Low- Density Lipoprotein, CIMT: Carotid Intima Media Thickness

Table 3. ROC analysis of patients for age, proteinuria and GFR; Logistic regression analysis of patients for age and proteinuria

CIMT ≥ 0.75 mm	AUC	95% C.I.		Cut-off	Sensitivite Spesifite	p
		Lower	Upper			
Age	0.737	0.638	0.836	60	%72.2 %64.4	<0.001
Proteinuria	0.639	0.525	0.752	500 mg/day	%64.4 %68.2	0.024

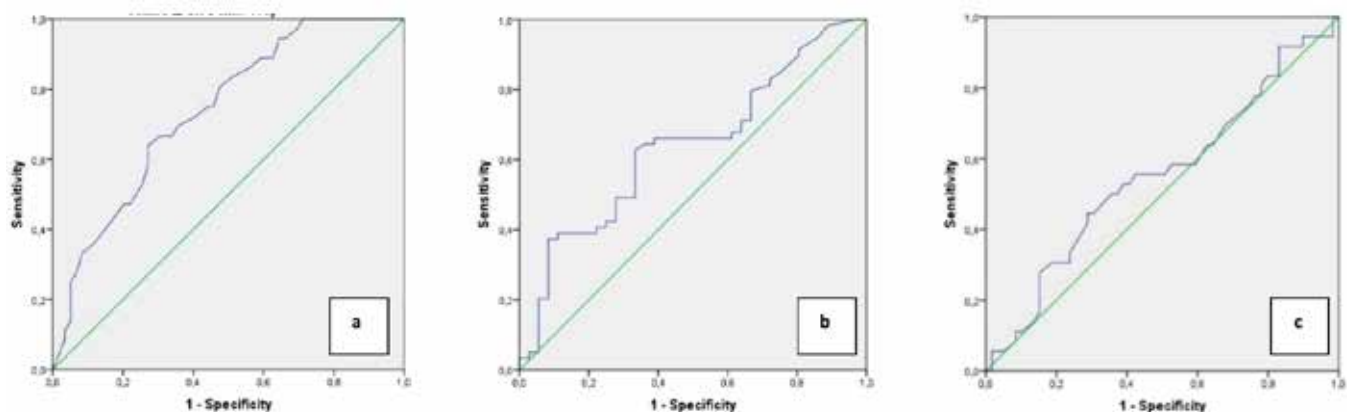| CIMT ≥ 0.75 mm	R²	βi	Odds ratio	95% C.I.		Wald	p
				Lower	Upper		
Age>60	0.104	1.414	4.113	1.694	9.985	9.761	0.002
Proteinuria >500 mg/day	0.044	0.891	2.437	1.042	5.704	4.219	0.036

Figure 1. ROC curves of the patients for age, proteinuria, and GFR

Discussion

Carotid intima-media thickness (CIMT) is an indicator of atherosclerotic vascular disease. It is considered a comprehensive picture of all changes in the arterial wall that occur over time and are caused by cardiovascular risk factors. In some studies, it has been found that CIMT is high in CKD at any age. It has been suggested that CIMT may be an indicator of cardiovascular and all-cause mortality in CKD cases. It has been shown that CIMT is significantly higher, especially in those with CKD over 50 years of age [15,16]. In our study, CIMT thickness was found to be significantly higher in CKD group. Of course, in this case, it should not be forgotten that age may also affect.

It is known that atherosclerosis and an increased risk of cardiovascular events occur from the early stages of CKD. As the CKD stage increases, this risk increases and CIMT increases significantly [17]. In our study, a significant difference was found between stage-3 patients and the control group, while no significant difference was found between stage-3, stage-4, and stage-5 patients. Systemic inflammation in CKD plays an important role in the development of atherosclerosis [18]. In addition, renal dysfunction changes the quality of the blood lipid profile, causing a more atherogenic lipid profile. Dyslipidemia in CKD is largely due to increased triglyceride levels, decreased HDL and altered LDL levels [19]. In our study, a significant difference in CRP levels was found between the patient and control group, which is an indicator of inflammation. While triglyceride levels were significantly higher in the patient group, HDL levels were significantly lower, and no difference was found in LDL and total cholesterol levels.

The presence of proteinuria is a powerful marker for the progression of chronic kidney disease, as well as an indicator of increased cardiovascular morbidity [20]. In a study by Momeni et al., a significant relationship was shown between proteinuria and CIMT in Type 2 DM patients [21]. In another study by Ito et al., a relationship was found between CIMT and GFR in patients with type 2 DM, but there was no relationship between proteinuria levels [22]. In our study, when comparing patients with and without type 2 DM, no significant difference was found between CIMT values in terms of both total and stages, but there was a significant difference between proteinuria levels. CIMT values were higher in CAD patients, as expected. In a study by Modi et al., in patients who were prepared for transplant, they observed that CIMT above 0.75 mm was a strong predictor for

CAD in patients with ESRD and that it could be used as a non-invasive screening test for pretransplant cardiac evaluation with its high sensitivity, specificity, and positive predictive value for these patients [14]. According to this value, we divided our patients into two groups. In the group with CIMT > 0.75 mm, age, female gender, and proteinuria levels were found to be significantly higher. However, no significant difference was found in the patients in terms of other parameters. It is an interesting result that there is no difference in terms of GFR and stages. The relationship between age and proteinuria with CIMT was evaluated with subsequent examinations. In our study, it was shown that the risk of atherosclerosis increased approximately 4 times in patients above 60 years of age, and the risk increased approximately 2.5 times in the presence of proteinuria above 500 mg/day. Our study has shown that the presence of proteinuria, independent of GFR in CKD, increases CIMT and thus cardiovascular mortality. We think that evaluation of patients with CIMT may be important in the early diagnosis of cardiovascular events, especially in elderly patients with proteinuria.

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